ETN



Docket No. BULK 3.0-029

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:
**Buchi Reddy REGURI, *et al.***

Group Art Unit: **1625**

Examiner: **Bernard I. Dentz**

Application No.: **10/662,980**

Confirmation No.: **2261**

Filed: **September 15, 2003**

For: **PROCESS FOR THE PREPARATION OF MONOKETALS OF 1,4-CYCLOHEXANEDIONE INCLUDING, 1,4-CYCLOHEXANEDIONE MONO-2,2-DIMETHYL TRIMETHYLENE KETAL**

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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

## TRANSMITTAL LETTER

To complete the requirements of the priority claim under 35 U.S.C. § 119 for the subject application, applicants are submitting herewith a certified copy of India Patent Application No. 681/MAS/2002, filed September 13, 2002.

If there are any questions regarding this submission, please contact the undersigned.

Respectfully submitted

Dated: November 10, 2005

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Attorney Docket No.: BULK 3.0-029



PTO/SB/92 (09-04)
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Application No.: 10/662,980
Filing Date: 09/15/2003
First Inventor: Buchi Reddy REGURI
Art Unit: 1625

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Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper. Documents enclosed:

Transmittal Letter - 1 pg.
Certified Copy of India Patent Application No. 681/MAS/2002 Filed 09/13/2002 - 11 pgs.
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# GOVERNMENT OF INDIA
# PATENT OFFICE
## Ministry of Commerce and Industry
## Department of Industrial Policy and Promotion

It is hereby certified that annexed here to is a true copy of **Complete Specification & Abstract** of the patent application as filed and detailed below:-

Date of application : **13-09-2002**

Application No : **681/MAS/2002**

APPLICANTS : **Dr. Reddy's Laboratories Limited, An Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, A.P., India**

In witness there of
I have here unto set my hand

Dated this the 14th day of October 2005
22th day of Asvina, 1927(Saka)

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FORM-2

THE PATENTS ACT, 1970

# COMPLETE SPECIFICATION

# (SECTION 10)



## An Improved process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal (An intermediate of Frovatriptan)



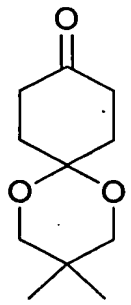
**Dr. Reddy's Laboratories Limited,**
**An Indian Company having its registered office at**
**7-1-27, Ameerpet,**
**Hyderabad-500 016, A.P., India.**



The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

**FIELD OF THE INVENTION:**

The present invention relates to an improved process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal, a key intermediate for many of the active pharma ingredients (API) including Frovatriptan, which is represented by the following Formula (1).



Formula (1)

**BACK GROUND OF THE INVENTION:**

1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal of the present invention is a key intermediate for the preparation of Frovatriptan, which is known anti-migraine drug.

**US 5,464,864** claimed Frovatriptan hydrochloride specifically and disclosed the process for the preparation, which doesn't involve the usage of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal of Formula (1) as an intermediate.

**US 5,618,947** claimed the process for the preparation of Frovatriptan succinate and also disclosed the process details, which involves the usage of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal of Formula (1) as an intermediate. The said patent doesn't disclose the process for the preparation of said intermediate of Formula (1).

**WO 99/54302** claimed the process for the preparation of enantiomers of Frovatriptan succinate and also disclosed the process details, which involves the usage of 1, 4-cyclohexane dione

mono–2, 2–dimethyl trimethylene ketal of Formula (1) as an intermediate. The said patent doesn't disclose the process for the preparation of said intermediate of Formula (1).

**Journal of Synthetic Communications 9(2), 123-127 (1979)** disclosed the process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal of the present invention. The process for the preparation comprises, Birch reduction of 4-methoxy phenol with Lithium, ammonia in presence of ethanol to yield 4-methoxy-3-cyclohexene-1-ol, which on further reaction with neopentyl glycol using PTSA in benzene medium gave 2,3-dimethyl–1,3-dipropylene ketal of 4-hydroxycyclohexanone. The resulting ketal on oxidation with pyridinium chlorochromate to yield the required 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal of the present invention, which is a key intermediate for the preparation of Frovatriptan. The major disadvantages associated with the process of above journal are usage of hazardous chemicals such as Lithium, ammonia and pyridinium chlorochromate, which are highly in compatible with moisture, in turn the process becomes hazardous and unsafe for commercial production as it may causes high explosion. The process also involves the usage of uncommon solvents such as ethanol as it is regulated and procuring in high volumes will be problematic, another solvent is benzene, which is carcinogenic.

**Journal of Synthetic Communications, 14 (1), 39-44 (1984)** disclosed the synthetic procedure for the synthesis of 1, 4-cyclohexane dione mono-2, 2-dimethyl trimethylene ketal and its related derivates. The process for the preparation comprises, continuous extraction of an aqueous solution of 1,4–cyclohexane dione containing 2,2-dimethyl –1,3-propane diol in molar excess and sulfuric acid as catalyst to afford the 1,4 cyclohexanedione mono –2,2 –dimethyl trimethylene ketal.

The disadvantage of the process disclosed in the above journal is the use of large volume of hexane, continuous extractions over a period of 41 hours renders the process uneconomical and hence it is not suitable for commercial production.

**Journal of Synthetic Communications, 4(3), 155-159 (1974)** disclosed the process for the preparation of 1,4-cyclohexane dione ethylene glycol of monoketal.

No other relevant references known in the art are disclosed the process for the preparation of 1,4–cyclohexane dione mono –2,2-dimethyl trimethylene ketal of Formula (1).

Hence these forgoing problems, directed us towards the present invention, which is an improved, convenient and cost-effective process for the preparation of 1,4–cyclohexane dione mono –2,2-dimethyl trimethylene ketal of the Formula (1). The compound of Formula (1) is a key intermediate for the preparation of Frovatriptan, a known active pharma ingredient for the treatment of migraine. Hence, the process for the preparation of compound of Formula (1) is required in a commercial feasible, cost-effective and non-hazardous.

The present invention provides a process for the preparation of 1,4–cyclohexane dione mono – 2,2-dimethyl trimethylene ketal in a simple, cost-effective, non-hazardous and it is also well suitable for commercial scale up.

**SUMMARY OF THE INVENTION:**

The present invention relates to an improved, convenient and cost-effective process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal, a key intermediate for the preparation of Frovatriptan. The process of the present invention comprises, condensation of 1,4–cyclo hexane dione and neopentyl glycol in C1-C3 halo alkane solvents, preferably dichloromethane or chloroform in presence of sulphuric acid as a catalyst.

The process of the present invention is simple, cost-effective, non-hazardous and is well suited for large-scale production.

**DETAILED DESCRIPTION OF THE INVENTION:**

The present invention relates to an improved process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal, a key intermediate for the preparation of Frovatriptan.

Accordingly, an improved process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal comprises of:

i. dissolving 1,4–cyclohexane dione and neopentyl glycol in C1-C3 halo alkane solvents such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, preferably dichloromethane or chloroform;

ii. adding an acidic catalyst such as sulphuric acid to the reaction solution of step (i);

iii. stirring the reaction mixture at 25-50$^{O}$C, preferably at 25-30$^{O}$C till the reaction completes;

iv. cooling the reaction mixture to a temperature of 0-25$^{O}$C, preferably 10-20$^{O}$C;

v. washing the reaction mixture of step (iv) with a known aqueous base solution;

vi. separating the organic layer from resulting biphasic mixture and distilling off the solvent till substantial completion under reduced pressure;

vii. adding aliphatic or alicyclic hydrocarbon solvent such as pertroleum ether, hexane, n-hexane, cyclohexane, n-heptane or cyclo heptane to the resulting residue;

viii. cooling the reaction mass to 0-25$^{O}$C, preferably 0-5$^{O}$C to filter the by-product;

viii. optionally distilling off the solvent from filtrate obtained in step (viii) till substantial completion under vacuum to yield the desired title compound in residual form or

filtering the separated solid from the concentrated mass to afford the desired title compound in solid form.

Thus, the compound 1,4 cyclohexane dione mono –2,2 – dimethyl trimethylene ketal obtained in the above process is a key raw material for the preparation of active pharma ingredients, which includes for the preparation of Frovatriptan. The process of the present invention is simple, cost-effective, and non-hazardous, is well suitable for commercial scale up.

It is noteworthy to mention that the starting raw materials 1,4 - Cyclohexane dione and Neopentyl glycol are outsourced in commercial quantities.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

**Preparation of 1, 4 Cyclohexane dione mono –2,2–dimethyl trimethylene ketal:**

**EXAMPLE-1:**

1,4 cyclohexane dione (20.0 grams) and neopentyl glycol (18.6 grams) were dissolved in dichloromethane (160 ml). Then sulphuric acid (3.2 grams) was added to the reaction solution at an ambient temperature and stirred till the reaction substantially completes, accompanied by cooling the reaction mixture to 10-20$^{O}$C. The resulting reaction mixture was washed with saturated aqueous sodium bicarbonate solution (80 ml) and separated the organic layer from the resulting biphasic mixture. The solvent was distilled off from organic layer till substantial completion under reduced pressure. Hexane (200 ml) was added to the resulting residual mass and followed by cooling the reaction mass to a temperature of 0-5$^{O}$C to filter the by-products. Then the solvent from the filtrate was distilled off till the substantial completion under vacuum to yield the desired 1,4 cyclohexane dione mono –2,2 – dimethyl trimethylene ketal.

(Weight: 22.9 grams)

**EXAMPLE-2:**

1,4 cyclohexane dione (25.0 grams) and neopentyl glycol (23.5 grams) were dissolved in chloroform (200 ml). Then sulphuric acid (4.0 grams) was added to the reaction solution at an ambient temperature and stirred till the reaction substantially completes, accompanied by cooling the reaction mixture to 10-20$^{O}$C. The resulting reaction mixture was washed with saturated aqueous sodium bicarbonate solution (100 ml) and separated the organic layer from the resulting biphasic mixture. The solvent was distilled off from organic layer till substantial completion under reduced pressure. Hexane (250 ml) was added to the resulting residual mass and followed by cooling the reaction mass to a temperature of 0-5$^{O}$C to filter the by-products. Then the solvent from the filtrate was distilled off till the substantial completion under vacuum to yield the desired 1,4 cyclohexane dione mono –2,2 – dimethyl trimethylene ketal.

(Weight: 29.0 grams)

**EXAMPLE-3:**

1,4 cyclohexane dione (25.0 grams) and neopentyl glycol (23.5 grams) were dissolved in dichloromethane (200 ml). Then sulphuric acid (4.0 grams) was added to the reaction solution at an ambient temperature and stirred till the reaction substantially completes, accompanied by cooling the reaction mixture to 10-20$^{O}$C. The resulting reaction mixture was washed with saturated aqueous sodium bicarbonate solution (100 ml) and separated the organic layer from the resulting biphasic mixture. The solvent was distilled off from organic layer till substantial completion under reduced pressure. n-Heptane (250 ml) was added to the resulting residual mass and followed by cooling the reaction mass to a temperature of 0-5$^{O}$C to filter the by-products. Then the solvent from the filtrate was distilled off till the substantial completion under vacuum to yield the desired 1,4 cyclohexane dione mono –2,2 – dimethyl trimethylene ketal.

(Weight: 30.0 grams)

**We claim:**

1. An improved process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal comprises of:

   i. dissolving 1,4–cyclohexane dione and neopentyl glycol in C1-C3 halo alkane solvents such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, preferably dichloromethane or chloroform;

   ii. adding an acidic catalyst such as sulphuric acid to the reaction solution of step (i);

   iii. stirring the reaction mixture at 25-50$^{O}$C, preferably at 25-30$^{O}$C till the reaction completes;

   iv. cooling the reaction mixture to a temperature of 0-25$^{O}$C, preferably 10-20$^{O}$C;

   v. washing the reaction mixture of step (iv) with a known aqueous base solution;

   vi. separating the organic layer from resulting biphasic mixture and distilling off the solvent till substantial completion under reduced pressure;

   vii. adding aliphatic or alicyclic hydrocarbon solvent such as pertroleum ether, hexane, n-hexane, cyclohexane, n-heptane or cyclo heptane to the resulting residue;

   viii. cooling the reaction mass to 0-25$^{O}$C, preferably 0-5$^{O}$C to filter the by-product;

   ix. optionally distilling off the solvent from filtrate obtained in step (viii) till substantial completion under vacuum to yield the desired title compound in residual form or filtering the separated solid from the concentrated mass to afford the desired title compound in solid form.

2. The process according to claim 1 of step (i), where in the haloalkane solvent is dichloromethane.

3. The process according to claim 1 of step (i), wherein the haloalkane solvent is chloroform.

4. The process according to claim 1 of step (i), wherein the mole ratio of 1,4- cyclohexane dione to neopentyl glycol is 1:1 to 4.

5. The process according to claim 4, wherein the mole ratio of 1,4-cyclohexane dione to neopentyl glycol is 1:1.

6. The process according to claim 1 of step (i), wherein the weight of 1,4- cyclohexane dione and volume of solvent is in the ratio of 1:1 to 20.

7. The process according to claim 6, wherein the weight of 1,4- cyclohexane dione and volume of solvent is in the ratio of 1:8

8. The process according to claim 1 of step (vii), wherein the aliphatic/alicyclic hydrocarbon solvent is hexane.

9. The process according to claim 1 of step (i), wherein the aliphatic/alicyclic hydrocarbon solvent is n-heptane.

10. The process for the preparation of 1, 4-cyclohexane dione mono–2, 2–dimethyl trimethylene ketal is substantially as herein described and exemplified.

Dated: 12th the day of September 2002

Signature) MBRe2004

Dr. R. Buchi Reddy,
Director (R&D),
Dr.Reddy's Laboratories Limited.

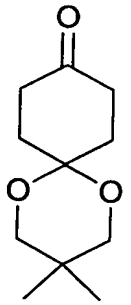
## ABSTRACT

**Title of the Invention:** "An improved process for the preparation of 1,4-cyclohexane dione mono-2, 2-dimethyl trimethylene ketal"
(An intermediate of Frovatriptan)

The present invention relates to an improved, convenient and cost-effective process for the preparation of 1,4-cyclohexane dione mono-2, 2-dimethyl trimethylene ketal, a key intermediate for the preparation of Frovatriptan, which is represented by the following Formula (1).

The process of the present invention comprises, condensation of 1,4-cyclohexane dione and neopentyl glycol in $C_1$-$C_3$ halo alkane solvents, preferably dichloromethane or chloroform in presence of sulphuric acid catalyst.

The process of the present invention is simple, cost-effective, non-hazardous and is well suited for large-scale production.



Formula (1)